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MALARIA

(CLINICAL FEATURES, TREATMENT, CONTROL AND PREVENTION)

DEPARTMENTS OF THE ARMY, THE NAVY, AND THE AIR FORCE
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(CLINICAL FEATURES, TREATMENT, CONTROL, AND PREVENTION)

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1. General. *a. Purpose.* This bulletin presents the latest available information on malaria and is meant to serve as a guide in the application of proper preventive, control, and therapeutic measures.

b. Definition and Synonyms. Malaria is the parasitic infection of vertebrates by protozoa of the genus *Plasmodium*. This publication is primarily concerned with malaria infection in man. Symptomatically, the disease is characterized in the acute stages by intermittent or remittent fever, profuse sweating, and chills. Chronic cases exhibit anemia, splenomegaly, and other serious, often fatal, complications. The condition has been called by many names—swamp fever, march fever, ague, miasmatic fever, and paludism. Often the term “fever” distinguished by the local place name has been used. The syndrome has been frequently named, either according to clinical periodicity or the species of causative parasite:

benign tertian, or vivax malaria, malignant tertian, subtertian, aestivoautumnal, E-A, or falciparum malaria; quartan malaria as caused by *P. malariae*; and ovale malaria.

c. History, Economic, and Military Importance. Malaria is a disease of great antiquity and is one of the most important preventable diseases of man. It was well described by Hippocrates in the third century before Christ; Celsus and Galen refer to it. Occurring throughout the tropical and subtropical areas of the world, it has postponed the development of large regions of the earth for centuries and has undermined the culture and welfare of many countries from ancient Greece to modern times. It has suppressed habitation of vast tracts of land and has held down the standard of living of great masses of people. It has prevented cultivation of millions of acres of rich soil, since the ability to work and the productivity of its victims are markedly impaired by the acute

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manifestations of the disease or the weakness, lassitude, and semi-invalidism which frequently accompany the chronic disease. Malaria was the most serious health hazard encountered by American troops in the South Pacific area during World War II, where about 100,000 men were infected and the success of the military campaign was jeopardized.

2. Etiologic Agent. *a. Classification.* Malaria in man is usually caused by one of the following members of the genus *Plasmodium*: *P. vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. The members of the genus are characterized by a complex life cycle, some stages of which can only be completed in the invertebrate host—the mosquito.

b. Life Cycle.

(1) *Exogenous cycle.* Females of certain species of *Anopheles* mosquitoes serve as the arthropod vectors for human malaria. Gametocytes of the malaria parasite ingested when the mosquito bites an infected person, develop into gametes in the stomach of the mosquito. These gametes are the sexual forms of the parasite and, by fusion of a sexual pair, produce a zygote. As this develops, it becomes a motile ookinete which penetrates the stomach walls of the mosquito and forms an oöcyst on the outer wall of that organ. By the process of sporogony a large number of sporozoites are produced. These migrate to the salivary gland of the mosquito and there they await transmission to the human host.

(2) *Endogenous cycle.* After transmission to man by the bite of an infected mosquito, the sporozoites enter the hepatic parenchymal cells and/or various reticuloendothelial cells. Here they develop into primary tissue schizonts which enlarge and segment, producing merozoites. The infected cells eventually rupture and the liberated merozoites may either enter other hepatic parenchymal cells and/or reticuloendothelial cells, or may enter the erythrocytes of the host.

(a) The course of the infection in the hepatic and/or reticuloendothelial cells varies with the species of *Plasmodium*. In the case of *P. falciparum* and *P.*

ovale the pre-erythrocytic phase consists of one generation or, at most, a few generations. In *P. vivax* or *P. malariae*, infection in the hepatic parenchymal and/or reticuloendothelial cells is believed to be able to last for several years. These are known as the exoerythrocytic forms, and may, at any time, produce merozoites capable of entering the host's erythrocytes and initiating the erythrocytic cycle.

(b) When the merozoites enter the erythrocytes they develop into small, ring-shaped trophozoites. These grow rapidly into schizonts and divide into erythrocytic merozoites. The infected erythrocytes eventually rupture, liberating the merozoites. This is the only part of the cycle which is associated with clinical disease. These merozoites enter other erythrocytes, reinitiating the cycle on a continuing basis. Some of these merozoites may develop into gametocytes (sexual forms) instead of schizonts. Gametocytes are of two types: the macrogametocyte (female) and the microgametocyte (male). When they are mature the gametocytes are able to infect mosquitoes, provided at least one of each type of gametocyte is ingested.

c. Morphology.

(1) *General.* Detailed differential characteristics of the various stages and species of the plasmodia that infect man can best be obtained from references containing colored plates illustrating types and development of plasmodia. (Army, see chapter 4, TM 8-227-2; USAF, see chapter 4, AFM 160-48.) The outstanding morphological characteristics of the different stages will be mentioned briefly as they appear in thin smears and are used in making a differential diagnosis. With Romanowsky stains, the cytoplasm of the parasites stains blue, the chromatin red. Within the four species mentioned above there are different strains. These have been established on clinical and chemo-

LIFE CYCLE OF PLASMODIUM THE MALARIA PARASITE

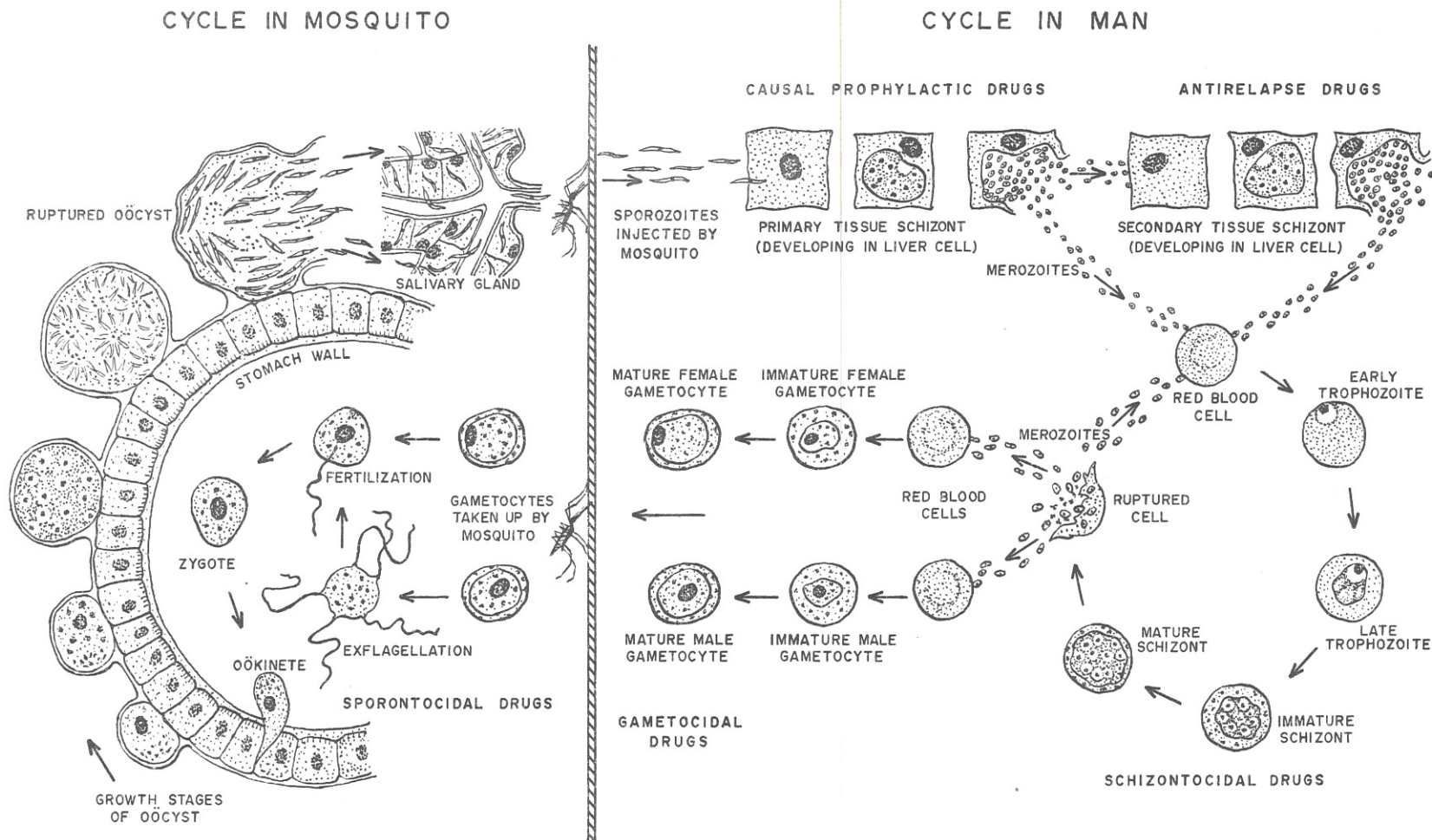


Figure 1

therapeutic grounds. They cannot be distinguished morphologically.

- (2) *P. vivax*. The early ring-shaped trophozoite is about one-third the size of the erythrocyte. As it grows, it may assume any shape due to the protrusion of pseudopodia. The erythrocyte begins to enlarge, red-staining Schüffner's dots appear in the infected cell, and small brown-pigment granules develop. The trophozoite eventually rounds up and almost fills the cell. The chromatin divides and 12 to 24 merozoites are formed. The microgametocyte is about the size of a normal erythrocyte and the chromatin is rather diffuse and near the center. The macrogametocyte is larger and the chromatin is compact and near the periphery.
- (3) *P. malariae*. The ring stage of this parasite is slightly smaller than that of *P. vivax* and more compact. The older trophozoite often extends as a band across the erythrocyte. Pigment granules are dark and large. The erythrocyte is not enlarged and the mature schizont almost fills it. Only 6 to 12 merozoites are formed and they are often arranged around a central mass of pigment, producing the daisy form, colloquially called the "rosette." The gametocytes are similar to those of *P. vivax*, but smaller.
- (4) *P. ovale*. This parasite is rare and resembles *P. vivax* in morphology. The trophozoites are more compact and sometimes form bands. The infected erythrocytes are enlarged and tend to be oval in shape. Generally, 8 merozoites are produced per cell and Schüffner's dots are conspicuous, intense, and numerous in every infected cell.
- (5) *P. falciparum*. The ring stage is small, and multiple infection of erythrocytes is common. The infected erythrocytes tend to be somewhat smaller than normal. Trophozoites more than half grown and schizonts do not usually occur in the peripheral blood. When mature schizonts do occur in the peripheral blood, generally 8 to 18 merozoites are present in each red cell. The gametocytes are elon-

gated and usually crescent shaped. The chromatin and pigment granules are usually centrally placed.

3. Epidemiology. a. Distribution.

- (1) *Geographical*. The geographical distribution of malaria is governed by suitable conditions for the breeding of efficient mosquito vectors and the influence of ambient temperature on the development of malaria parasites within the mosquitoes. Rainfall, humidity, and temperature ranges are important factors. Most of the endemic areas lie between 45° north and 40° south latitude. *P. falciparum* is found predominantly in the tropic zones. *P. malariae* is spotty in distribution and comparatively rare; it occurs in both the tropic and temperate zones. *P. ovale* is rare but has been reported from widely separated areas, including the Philippines, South America, and parts of Africa. *P. vivax* is more widely distributed than the other types.
- (2) *Racial*. All races of man are susceptible to malarial infection; Negroes appear to be more resistant to *P. vivax* infection than Caucasians.

b. *The Vector*. Human malaria is transmitted by anopheline mosquitoes. Of the approximately 200 species described, only about 60 have been incriminated as vectors. This should not be interpreted to mean that only 60 species of anophelines can serve as vectors or that they are equally proficient in malaria transmission. In a given area, there may be more than one vector species but usually a single species assumes the major role. This relationship in one area does not necessarily mean that it will be the same in another and modification of the environment may cause a change in the relative importance of the vectors. Most anophelines bite at night or during twilight. The breeding and feeding habits vary with the species of mosquito involved. The transmission of malaria is usually closely associated with breeding places of the vector. Unless the vectors for each area and their habits are known, the problem of control cannot be undertaken with any degree of confidence. For example, swamp drainage would be of little value in controlling a vector

which breeds in water-collecting epiphytes that grow in trees, or in controlling *Anopheles minimus* which breeds at the sides of running hill streams (1,000 to 3,000 feet altitude) in the Philippines and South Vietnam. The elimination of an anopheline that prefers feeding on animals other than man would have little effect on the incidence of malaria. House spraying with residual insecticides is not effective if the mosquito vector does not rest on the treated walls. For these reasons it is important to seek the advice and services of medical entomologists.

c. Mode of Transmission. (1) *General.* The anopheline mosquito acquires its infection by biting a person whose blood cells contain mature gametocytes of a *Plasmodium*. Man usually acquires infection by the bite of an infected mosquito. It should be remembered, however, that the infection can also be transmitted directly, e.g., by blood transfusion or contaminated needle or syringe.

(2) *Communicability.* Man can transmit the infection to the mosquito vector only if microgametocytes and macrogametocytes are both present in his blood stream in sufficient number so that the vector acquires at least one of each type of gametocyte during a blood meal. Early in the initial infection of man mature gametocytes are usually not present in sufficient numbers to make transmission of infection to the mosquito likely. In untreated cases a suitable concentration generally develops in time and remains for months. Gametocytes may also be present in treated asymptomatic cases and in patients that have relapsed. The onset of communicability in the mosquito is affected by temperature, the mosquito species, and the species of *Plasmodium*. Under optimal conditions it requires 7 to 14 days after the infecting blood meal for *P. vivax* and *P. falciparum*, and somewhat longer for *P. malariae*, for the mosquito to become infective for man.

(3) *Incubation period.* The incubation period in man varies with the species of *Plasmodium*, the number of sporozoites injected, and the amount of resistance to the invasion. The average incubation period in *P. vivax*, *P. ovale*, and *P. falciparum*

infections is 11 to 14 days. In *P. malariae*, it is usually much longer and averages 23 days.

d. The Reservoir. There is some experimental evidence that human malaria can be artificially transmitted to monkeys and vice versa. Although a naturally acquired infection with a species of monkey malaria has been reported in man, it is not known, as yet, whether monkey malaria constitutes an important zoonosis. In endemic areas, humans probably serve as the sole reservoir. There, infected persons often with parasitemia without severe clinical symptoms because of the partial immunity that has developed, serve as a source of infection for the local vectors. When susceptible persons are introduced into such an area, malaria will appear in epidemic proportions among them unless suitable control measures are taken.

e. Host-Parasite Relationships.

(1) *General.* For about 6 days after the introduction of sporozoites into man, development of the parasite takes place in liver parenchymal cells and/or reticuloendothelial cells. On the 6th to 9th day the first invasion of the erythrocytes occurs. Trophozoites become sufficiently numerous to be demonstrated microscopically on the 8th to 15th day. Clinical symptoms usually appear 2 or 3 days after the parasitemia begins to develop. The destruction of the erythrocytes produces a secondary anemia; other effects of the parasite on the host vary with the species.

(2) *P. vivax.* The merozoites of this species attack young erythrocytes and this tends to limit the parasitemia. The number of organisms usually ranges from 8,000 to 20,000 per ml. (from 0.2 to 4.0 percent of erythrocytes). Gametocytes usually appear in the peripheral blood early in the course of the infection. Initially there are apt to be two concurrent asexual cycles, giving paroxysms every day. One of these eventually disappears and the characteristic pattern of "tertian" malaria becomes evident. If untreated, the pattern in the patient may revert from time to time to that seen in the early stages of the disease; there may also be a

series of remissions and recrudescences for a period of 3 to 4 months. With this species, the exoerythrocytic portion of the cycle usually continues for a period of years in the parenchymal tissues. Thus, relapses may occur after recovery from the first series of attacks, or after treatment that eliminates only the erythrocytic stages. These relationships vary with the strain of the organism.

- (3) *P. malariae*. The parasitemia in infections with this species is due to invasion of aging erythrocytes and is thus also limited. The number of organisms usually does not exceed 10,000 per ml. (2 percent of erythrocytes). Gametocytes are usually sparse. Early in the course of the infection there is only one asexual cycle present and the patient's paroxysms recur at intervals of 72 hours. Later other cycles may appear and febrile episodes become more frequent. The relationship between the exoerythrocytic and the erythrocytic phases is apparently like that of *P. vivax*.
- (4) *P. falciparum*. The merozoites of this parasite attack erythrocytes of all ages. This characteristic makes it the most dangerous of the malarial parasites thus requiring rapid diagnosis and treatment to prevent fatalities. Parasitemia may rapidly become extremely high. The prognosis is grave when counts of 500,000 parasites per ml. occur (10 percent of erythrocytes). For this reason it is important to follow the parasitization in thick blood smears to insure therapy is having an effect, and not to permit this level of parasitemia to occur. Schizogony in this species requires 48 hours but it is less synchronized than in the others. For this reason the patient's paroxysms may be almost continuous. The infected erythrocytes tend to agglutinate and adhere to the capillary endothelium. Thrombi and emboli are not uncommon. Gametocytes may appear in the peripheral blood about 10 days after the onset of symptoms and are infective to mosquitoes several days later. In untreated

patients that survive the attacks, the number of trophozoites tends to decrease as the number of gametocytes increases. There apparently are no persisting exoerythrocytic forms in infections with *P. falciparum*, so that elimination of asexual erythrocytic forms by administration of adequate doses of only a blood schizonticide may result in the *complete* elimination of parasites from the body (radical cure).

- (5) *P. ovale*. This species follows the same pattern as that seen in *P. vivax*, except that the exoerythrocytic phase is apparently short. It usually produces relatively mild attacks of short duration. Because of this relationship radical cures are common.
- (6) *Mixed infections*. It is possible that any combination of mixed infections could be acquired, but that of *P. vivax* with *P. falciparum* is the most common. In such cases, if the infections were acquired at the same time, *P. falciparum* appears first and the clinical symptoms follow the pattern given above. Eventually *P. vivax* gains the ascendancy and the other species decrease in numbers. This is followed by alternating dominance of first one species and then the other, giving almost continuous clinical evidence of the disease in one form or the other.

f. Immunity. With repeated infections a person acquires a tolerance to the species and strain he has had. Evidence of resistance to the infection is usually shown by milder clinical symptoms and a shorter course. In an endemic area, this is shown by the fact that the children and young adults most commonly have parasitemia and symptoms while older persons may show negative smears, or, if parasitized, often are asymptomatic. A person who has acquired some degree of immunity against one strain and is then exposed to another usually develops the disease, but its course may be somewhat modified. There is no true cross-immunity between species of *Plasmodia*.

4. Pathology. *a. General.* Malaria is accompanied by the destruction of enormous numbers of erythrocytes with resultant anemia, increased

serum bilirubin, and deposition of malarial pigment in the reticuloendothelial cells. The latter produces the characteristic slaty or blackish pigmentation of the spleen, liver, and brain. Enlargement of the liver and spleen is common. The spleen may weigh from 300 to 700 grams; weights over 1,000 grams have been found in chronic vivax infections. A rare complication is intra-abdominal hemorrhage from rupture of the taut capsule of an enlarged spleen. If an antemortem diagnosis of malaria had been made in a case of spontaneous splenic rupture, it is important, at autopsy, to make thin impression smears of the spleen, liver, and bone marrow. These should be fixed in methyl alcohol and stained by Giemsa's or Wright's methods so that an examination for intra-erythrocytic parasites can be accomplished.

b. Falciparum Malaria. In fatal falciparum malaria, there is an intense concentration of parasitized erythrocytes in the capillaries of many organs. Increased viscosity and slowing of the blood flow in capillaries, combined with the marked tendency of the infected erythrocytes to adhere to capillary walls, leads to thrombi. The slate-gray color of the cerebral and cerebellar cortex, which is characteristic of cerebral malaria, is due to the plugging of the capillaries by parasitized erythrocytes, phagocytic cells and occasional free parasites. "Ring" hemorrhages often encircle the packed capillaries in the brain. The diarrhea which occurs in some cases is probably due to obstruction of the mucosal circulation by plugs of infected erythrocytes in the capillaries. The kidneys in those patients with falciparum malaria who clinically show hemoglobinuria reveal the histologic features of lower nephron nephrosis. These features are similar to the changes seen in patients dying of transfusion reactions. In many cases of falciparum malaria, the cause of death cannot be explained by the changes seen in any organ.

5. Clinical Characteristics. *a. Vivax and Quartan Malaria.* Prodromata consist of malaise, muscle aches, headache, anorexia, and slight fever. The acute phenomena begin with an abrupt onset with rigor, varying from slight chilliness to a frank chill accompanied by a sensation of extreme cold, although the temperature rises rapidly to 104°-106° F. The pulse is thready and rapid; polyuria, nausea, and vomiting are common. The

"hot stage" begins within 60 minutes. It is usually accompanied by severe headache, extreme thirst, epigastric discomfort with nausea and vomiting becoming more severe, and frequently by mild delirium. This stage is followed by a profuse diaphoresis, lasting 2 to 3 hours, and a rapid fall in temperature. After a period of several days in untreated cases of vivax malaria, the parasites mature on alternate days and the clinical attacks, therefore, occur every other day. In quartan malaria, schizogony, with the accompanying display of clinical symptoms, occurs every 72 hours.

b. Falciparum Malaria. The onset is frequently insidious with the appearance of headache of increasing severity and gastrointestinal symptoms. In other cases, the onset may be abrupt with a sensation of chilliness rather than a frank chill, a prolonged intensified "hot stage," and a gradual fall in temperature without marked diaphoresis. The hyperthermia may be prolonged, with a double-peaked elevation. Prostration is usually marked and delirium is common. Falciparum malaria is notorious for the sudden and dramatic appearance of severe and dangerous forms of the disease which can rapidly cause the death of the patient if the condition is not promptly diagnosed and treated. Three chief clinical types have been noted.

- (1) *Bilious Remittent Fever.* Sudden onset with severe nausea and profuse, continuous vomiting. Icterus usually appears on the second day, and is accompanied by epigastric and liver tenderness. Hematemesis is not uncommon and may be associated with an elevated blood urea nitrogen.
- (2) *Cerebral Malaria.* The onset may be sudden or gradual. The patient may complain of progressively increasing headache, with little or no fever, and gradually lapse into coma; or there may be an uncontrollable rise of temperature in excess of 108° F. leading rapidly to a fatal termination. Papilledema is commonly seen and may be a valuable prognostic sign. Occasionally there is mania or acute psychosis. Corticosteroids have been reported to be of benefit to patients with cerebral malaria and

may be used in severely ill patients manifesting evidence of adrenal cortical insufficiency or unresponsive blackwater fever.

- (3) *Algid Malaria*. Profound prostration with a tendency of fatal syncope, marked coldness of skin with high internal temperatures, severe hemolytic anemia, and intense diarrhea. This is synonymous with the current term "medical shock".

c. Blackwater Fever. Blackwater fever is one of the most serious complications of malaria, chiefly that due to *P. falciparum*, and is characterized by prostrating chills, usually sudden in onset, profuse vomiting, icterus appearing within a few hours of onset, the passage of dark red to black urine, and a rapidly developing anemia. It is an acute intravascular hemolysis with hemoglobinemia, hemoglobinuria, and renal insufficiency. The cause of the hemolysis is unknown. Predisposing factors are thought to be: repeated falciparum infections; irregular therapy with antimalarials—especially quinine; previous attacks of hemoglobinuria; sensitization to the malaria parasite; fatigue and chilling. Standard texts (see app. I) should be consulted for a more detailed discussion of the condition. The presence of the three cardinal symptoms (hemoglobinuria, fever, and icterus) in a patient known to have had malaria, is strong presumptive evidence of blackwater fever. The mortality ratio is 25 to 50 percent. Absolute bed rest is essential in treatment; *such patients should not be evacuated* unless use of the artificial kidney becomes mandatory, in which case it would be better to transport an artificial kidney and team to the patient, if possible. Meticulous attention must be given to the maintenance of fluid and electrolyte balance. Transfusion of whole blood or, preferably, packed erythrocytes is beneficial. Chloroquine hydrochloride given slowly intravenously is the drug of choice. *Atabrine, primaquine and any of the other 8-aminoquinolines, alkalies and diuretics are contraindicated*. The use of quinine in other than drug-resistant infections is contraindicated. If intravenous chloroquine does not reduce parasitemia, then there should be a strong index of suspicion that the blackwater fever is due to a resistant organism.

The prognosis then is more grave and every effort should be made to stabilize the patient, main-

tain fluid and electrolyte balance to prevent oliguria and anuria; combat anemia by daily transfusions with packed erythrocytes if necessary. The use of quinine, intravenously if necessary, may be warranted. After convalescence is established, careful observation for persisting parasitemia is essential. If found, quinine should be used to effect a radical cure, but careful watch should be maintained for recurrence of hemoglobinuria. Patients who have had blackwater fever should be evacuated from and not be returned to any area where malaria is endemic.

6. Prognosis. The prognosis for recovery from the primary attack is excellent in malaria due to *P. vivax*, *P. malariae*, or *P. ovale*, although relapse is common in inadequately treated *P. vivax* infections. Adequately treated falciparum malaria carries a good prognosis; the mortality may be 25 percent in untreated patients.

7. Diagnosis. *a. General.* Malaria causes symptoms which may mimic a wide range of diseases. It should be suspected in illnesses characterized by periodic chills and fevers, in any obscure condition with or without fever in endemic regions, and also, in poorly defined sickness in personnel who have served in endemic areas. **THE CLASSICAL PICTURE OF REGULAR CHILLS AND FEVER IS INFREQUENT AMONG TROOPS WHO HAVE RECENTLY BEEN TAKING SUPPRESSIVE MEDICATION.** The triad of headache, backache, and fever with or without chills, is the commonest symptom complex in these individuals. Furthermore, in recently exposed persons, delirium, coma, or medical shock should immediately suggest the possibility of malaria. Even in severe cases, the temperature may be subnormal. Other previous diagnoses should not be allowed to mislead the observer. Clinical disease due to malaria not infrequently coincides with other illnesses or injuries or operative procedures. Clinical attacks may recur after treatment or the initial evidence of disease may appear weeks after discontinuing suppressive drug administration. In summary, *whenever the possibility of malaria exists, the diagnosis must be considered no matter what clinical picture is presented.*

b. Laboratory Findings.

- (1) *General.* The clinical diagnosis of malaria is generally confirmed by the demonstration of malarial parasites in smears

or films of the peripheral blood of the patient. The accuracy of diagnosis by examination of either thick or thin smears (Army, for method of preparation see chapter 4, TM 8-227-2; USAF, see chapter 4 AFM 160-48) depends largely on the competency and experience of the person making them as well as the perseverance and thoroughness of the search. Repeated thick film studies are often necessary before the parasites are found. Inexperienced personnel commonly err in mistaking blood platelets for plasmodia. In the tropics, molds and bacteria growing in the stains are a frequent source of confusion. Both thick and thin blood smears should be obtained from all cases of suspected malaria for microscopic examination. Thick smears should be examined as soon as possible, each being studied for at least 10 minutes without the parasite being found before smear is declared negative. Thin smears should be studied for at least 20 minutes before they are deemed negative. With very few exceptions, the first or second examination will reveal parasites in the blood from cases of malaria with clinical symptoms. If parasites are not found and malaria is still suspected, smears should be made at 6-hour intervals for several successive days, as symptoms of the first attack may appear when the density of parasites in the circulating blood is low, particularly in falciparum infections. Parasites are generally more numerous in relapses than in primary attacks. Suppressive therapy, terminated some time in the past, does not appear to reduce significantly the chances of finding parasites in thick films in vivax malaria. In heavy falciparum infections, the proportion of parasitized erythrocytes should be estimated, since this is helpful in prognosis.

- (2) *Species diagnosis.* Knowledge of the species of the causative parasite is valuable in determining therapeutic management of a case. The diagnosis of falciparum malaria requires close observation

of the patient for the onset of symptoms of underlying dangerous pathology and also provides information that repeated relapses are unlikely. In contrast, the diagnosis of vivax malaria informs the physician that the disease is not likely to become suddenly dangerous and that repeated relapses may be expected unless appropriate curative therapy is administered.

- (3) *Smears of blood.* Smears from suspected patients should be made, when possible, for later study whenever military operations, lack of laboratory facilities, or clinical urgency make it necessary to give antimalarial chemotherapy without prior laboratory confirmation of the diagnosis. They should accompany the patient's medical records if he is transferred.

8. Treatment of Clinical Disease. Overt illness is due to the continued maturation and release of the erythrocytic asexual forms of the malaria parasites. Treatment of clinical disease is aimed toward the reduction in number or the elimination of these forms. The principles of treatment are identical for primary attacks or for recurrences in humans infected with any of the malaria species. Normally the oral route of administration of drugs is preferable. However, each patient must be evaluated in terms of the degree of response to oral medication, the duration of illness prior to recognition, the clinical status, and the response of other patients coming from the same area to the drugs available for therapy. (The dosages described below are for adults and should be reduced on a weight basis for children.)

a. Chloroquine (4-aminoquinoline).

- (1) *Oral administration.* An initial dose of two chloroquine phosphate tablets (1 gram of chloroquine phosphate—600 mg. of chloroquine base), should be followed in 6 hours by one chloroquine tablet (0.5 gram of chloroquine phosphate—300 mg. chloroquine base). Subsequently one tablet is given daily for the next 2 days. Thus, four doses are given over a period of 3 days for a total of 2.5 grams of chloroquine phosphate (1.5 grams of chloroquine base).

(2) *Parenteral administration.* In critically ill patients and/or when oral medication is not feasible, chloroquine hydrochloride may be used. The contents of one ampule (250 mg. of chloroquine hydrochloride—200 mg. of base in 5 ml. of unbuffered sterile distilled water) is given *intramuscularly*. This may be repeated at 6-hour intervals but the total parenteral dosage in the first 24 hours should not exceed four ampules (1 gram of chloroquine hydrochloride—800 mg. of chloroquine base). The same drug can be given *slowly* intravenously in the above dosage diluted with 40 ml. sterile physiological saline. Such therapy is rarely, if ever, indicated since toxicity is increased, and the response to intramuscular injection is so rapid. However, for blackwater fever, chloroquine hydrochloride given intravenously is the treatment of choice. Oral administration of the drug should be substituted or resumed as soon as possible.

(3) *Toxicity.* Toxic manifestations occur infrequently. Mild transient headaches, pruritis, anorexia, blurring of vision, vertigo, diarrhea, malaise, and urticaria have been noted. Severe toxicity may be combated by administering ammonium chloride orally until the urine gives an acid reaction.

(4) *Drug resistant strains.* The existence of drug resistant strains of *P. falciparum* in Colombia, Brazil, and southeast Asia is well established and documented (app. I). These strains show varying to complete resistance to the 4-aminoquinolines (including chloroquine), and this resistance crosses to all of the other available synthetic antimalarials, leaving quinine as the only effective drug. In treating clinical cases of malaria with chloroquine in these areas, particularly where the species has been established as *P. falciparum*, careful observation of the patient and his response to therapy is mandatory. Marked increases in parasitemia occurring despite adequate levels of chloroquine, or transient decreases only in fever

or parasitemia, are indications that these cases should be treated with quinine as outlined in *b* below. They should be observed closely, clinically and parasitologically, for a minimum period of 14 days following completion of therapy. Should recrudescence of falciparum malaria occur following chloroquine treatment, quinine treatment as outlined in *b* below should be instituted.

b. Quinine. This compound may be used alone or as a supplement to the 4-aminoquinolines in the treatment of malaria. Quinine reaches high blood concentration rapidly and is not fixed in the tissues. In areas where falciparum malaria occurs, quinine is frequently the drug of choice when rapid action by intravenous administration is imperative. This is especially true when the patient is comatose or when the blood film shows a high population of *P. falciparum* (more than 10 percent of the red cells infected). However, quinine is contraindicated in blackwater fever unless it appears that a drug-resistant strain is involved.

(1) *Oral administration.* Quinine sulfate, three 5-grain tablets (0.975 gram) three times daily after meals for 2 days, followed by two 5-grain tablets (0.650 gram) three times daily after meals for 8 days. Care must be exercised not to use old tablets of quinine which may have hardened and therefore fail to disintegrate in the bowel.

(2) *Intravenous administration.* One 2-cc. ampule of quinine dihydrochloride, injection, N.F. (containing 300 mg. (5 grains) per cc.) is diluted in 300 cc. of normal saline, glucose-saline, plasma, or other intravenous fluid appropriate to the patient's state of hydration and electrolyte balance, and given slowly (not less than 30 minutes), since hypotension may occur if it is injected intravenously too rapidly. The blood pressure and pulse should be monitored constantly to detect hypotension or arrhythmia. It may be repeated every 6 to 8 hours as necessary but not more than three such doses (a total of 30 grains of quinine dihydrochloride) should be administered during a 24-hour

period. Oral administration should be substituted or resumed as soon as possible.

- (3) *Readministration.* Should recrudescence of falciparum malaria occur after treatment with quinine, readministration of quinine sulfate as outlined above may be required for from 10 to 21 days.
- (4) *Toxicity.* Cinchonism is characterized by disturbances of the central nervous system which may take the form of depression, giddiness, headache, tinnitus, deafness, amblyopia, confusion, somnolence, or blindness. Alleviation is achieved by withdrawing the drug.

c. Alternate Chemotherapeutic Agents.

- (1) *Amodiaquine.* A 4-aminoquinoline with action comparable to that of chloroquine which is given orally in the same regimen and dosage (not a standard item).
- (2) *Quinacrine (Atabrine).* A 9-aminoacridine which is generally considered less active than the 4-aminoquinolines. It is administered orally over 7 days in five divided doses of 200 mg. each (for a total of 1 gram of quinacrine hydrochloride) on the first day, and 100 mg. three times daily for the next 6 days. Primaquine should not be used concurrently with quinacrine or within 3 weeks after its termination.

d. General Care. Fluid intake, appropriate to the climate, should be maintained, using the intravenous route if necessary. Electrolyte imbalance should be corrected. Sweetened tea and fruit juices are well accepted. When the patient is unable to take food by mouth, 5 percent glucose in physiological saline should be given intravenously. A word of caution here, some patients have an intense thirst and, if not properly supervised by limiting the intake of fluids, can literally develop water intoxication. The recording of daily body weight may assist in the recognition of unsuspected water loading. A well-planned diet containing at least 150 grams of protein daily with vitamin supplements should be given as soon as tolerated.

e. Aftercare.

- (1) *Persistent Asymptomatic Parasitemia.* After the temperature has returned to normal levels some patients will continue

to circulate asexual forms of the parasite. Some success has been achieved in eliminating these by the concurrent administration of pyrimethamine, 50 mg. per day for 3 days, and sulfadiazine, 2 grams per day (in divided doses) for 5 days. This combination is slow acting and has no place in the treatment of acute disease.

- (2) *Resumption of Prophylaxis.* After therapy is completed all patients should resume the chemoprophylactic regimen in use in their particular locality (see para 9j). If they are leaving the endemic area, they require the same continuing prophylaxis required for all personnel leaving the area.

- (3) *Hazard of Transmission to Others.* In endemic areas the major source of infection to mosquitoes is the chronically infected indigenous population. Thus, the presence of a comparatively few infected military personnel in an endemic area does not materially increase the risk of infection to others. Quarantine of military personnel in endemic areas is meaningless. In nonendemic areas, or at base camps in endemic areas where environmental controls are in effect, where species of *Anopheles* mosquitoes exist, treatment of malaria will be on an inpatient basis where assurance of proper supervision of chemotherapy and appropriate environmental control measures will reduce the possibility of introduction or reintroduction of malaria.

- (4) *Treatment for Radical Cure—Nonendemic Areas.* In nonendemic areas, where chemoprophylaxis is not required, it becomes important to insure that the secondary or persisting exoerythrocytic forms of *P. vivax* and *P. malariae*, and to lesser extent *P. ovale*, are destroyed. Therefore, after clinical cure of infections with these species (or mixed infections of these species) the following regimen should be employed:

- (a) The combined chloroquine-primaquine tablet (0.300 gram of chloroquine base and 0.045 gram of primaquine base) should be given *on the same day* of each

week for a *minimum* of 6 weeks, and preferably for 8 weeks. This is the regimen of choice and has the advantage over the alternate regimen in that weekly therapy mitigates the hemolytic effect (in G6PD-deficient individuals).

- (b) The alternate regimen is one tablet of primaquine phosphate daily for 14 days (each 26.3 mg. tablet of primaquine phosphate contains 15 mg. of primaquine base), and may be used when the regimen of choice is not practical. It should be started concurrently with chloroquine, given as described in (a) above. Pilots, aircrews, and other personnel on flying status may take the combined chloroquine-primaquine tablet weekly, but if the alternate regimen for eradicating the tissue stages of malaria infection is used, that is, a primaquine tablet (15 mg./m. base) daily for 14 days, then such personnel will be grounded for that 2-week period and until there is assurance that red blood cells and hemoglobin are normal.
- (c) Primaquine has a relatively narrow margin of safety between effective and toxic doses, especially in dark-skinned individuals. The toxic symptoms range from gastric distress to severe hemolytic reactions. The latter occurs in persons having erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency. Severe toxicity is rare in those receiving the recommended dosages. In the sensitive individual, daily doses of 15 mg. of primaquine will produce a self-limiting hemolysis, by virtue of the fact that the younger erythrocytes are relatively resistant to destruction by the drug. Weekly administration of 45 mg. of primaquine (combined with chloroquine) should very rarely produce a transient clinically demonstrable hemolysis in sensitive adults. If administered for 8 weeks it will produce a radical cure of vivax infections in 90 percent of cases. Quinacrine (atabrine) tends to poten-

tiate the toxicity of primaquine and should not be given concurrently, nor should a course of primaquine be started within 3 weeks of terminating a course of quinacrine.

9. Prevention and Control. *a. General.* Measures for the prevention and control of malaria fall into two categories:

(1) *Prevention of bites by mosquitoes.*

(a). Control of the mosquito and its environment.

(b) Individual protective measures.

(2) *Therapy.*

(a) Chemoprophylaxis.

(b) Effective early treatment of cases.

b. Selection of Measures.

- (1) Under highly mobile tactical situations, it may be necessary to depend upon chemoprophylaxis, supplemented by whatever individual protective measures are practicable and consistent with the attainment of the military mission. This course must be considered a calculated risk especially if other mosquito-borne diseases such as dengue, filariasis, encephalitides, etc., against which no protection is afforded by medicinal suppression of malaria, are prevalent in the area. The nuisance and actual debilitating effects of heavy mosquito biting must not be underestimated.
- (2) Under stabilized conditions in other than highly malarious areas, it may be possible to achieve control by environmental methods alone.
- (3) Even under stabilized conditions, in highly malarious areas, chemoprophylaxis should be included in the control measures.

c. Command Responsibility. It is a command responsibility to decide upon the malaria control measures to be adopted for any given area, period, and mission.

d. Medical Service. The military medical services are charged with the responsibility of investigating and determining the factors which affect the health of military personnel and with recommending and supervising measures for the con-

control and prevention of disease in military personnel, civilian personnel under military jurisdiction, and among inhabitants of occupied territory. In advising commanders, the following principal factors should be considered:

- (1) The military mission, estimated duration, and seasons.
- (2) Malarious nature of the area during the mission.
- (3) The biology of the local mosquito vectors and their susceptibility to insecticides.
- (4) Control measures effected by local civilian health agencies.
- (5) State of training of troops.
- (6) Prevalence of other mosquito-borne or arthropod-borne diseases for which effective chemoprophylactic measures are not available.
- (7) The supply and distribution of effective insecticides and dispersal equipment.

e. Engineering Service (Corps of Engineers, Army; Civil Engineering Service, Air Force; and the Bureau of Yards and Docks, Navy).

- (1) The Engineering Service is responsible for insect and rodent control operations at—
 - (a) Posts, camps, stations and bases within the United States and
 - (b) In oversea areas under static noncombat conditions when engineering services are established.
- (2) The Medical Service has the responsibility of conducting surveys to determine the requirements and the efficiency of control operations, assisting commanders and supply personnel in establishing requirements and control levels for effective insecticides and dispersal equipment.

f. Organization for Malaria Control.

- (1) *Army and Air Force vector control details.* Regulations direct that under certain conditions the commanding officer of each company, battery, wing, group, squadron, or similar unit appoint a vector control detail (Air Force) or field sanitation team (Army) to provide insect and rodent control within his area of responsibility. This detail should consist of at least two enlisted men, one of whom

should be a noncommissioned officer. Units having organic medical personnel will utilize them as members of the field sanitation team. In a combat zone or communications zone prior to the establishment of Engineer Repairs and Utilities Services, the Medical Service will supervise and execute all required control operations which are beyond the capabilities of unit vector control details.

- (2) *Army Preventive Medicine Units.* In order to carry out the above responsibilities, TOE Preventive Medicine Units have been established as follows:

- (a) The Preventive Medicine Unit (Service) (Field) is assigned to support a field army or a theater army logistic command, to provide technical supervisory personnel for the field study, evaluation, and control of environmental and other factors affecting the health and morale of troops in the field. The medical problems and the tactical situation usually necessitate assigning these units on the basis of one per Army Corps or logistic command.
- (b) The Medical Detachment (Preventive Medicine Control) (Separate) provides technical personnel for the control of disease vectors or reservoirs, and related environmental hygiene functions in a division area, or an area with a similar military population.
- (c) The Medical Detachment (Preventive Medicine Survey) (Separate) provides technical personnel for the field study, survey, and evaluation of disease vectors and reservoirs, and related environmental health problems in an Army Corps or in a military population equivalent to a corps.
- (d) The preventive medicine units provide an essential service by training the personnel in the field sanitation teams and supervising their operations. The preventive medicine personnel should closely monitor the supply and distribution of pesticides and dispersal equipment and insure that the program

is conducted smoothly and effectively. These units should be assigned so they are responsive to the Command Surgeon.

- (3) *Navy.* Vector survey and control responsibilities are assigned to preventive medicine units, which may operate independently and areawide in the case of naval shore-based forces, or as an integral portion of the organization of a division in the case of Marine Corps forces. Responsibilities and functions are essentially as given under (1) and (2) above. Current directives of the Bureau of Medicine and Surgery should be consulted.
- (4) *Air Force.* Epidemiological flights provide epidemiological services only as a part of comprehensive theater medical service to base, area, and unit commanders. (See OT 3046 and AFR 160-119.)

g. Control of the Mosquito and its Environment. Environmental control measures include proper selection of camp and base sites, mosquito-proofing, the destruction of adult mosquitoes, and the control of mosquito breeding. These measures have their greatest usefulness at permanent or semipermanent installations, but should be applied as far forward as the military situation permits. From 4 to 6 weeks will elapse before measures to control mosquito breeding will materially reduce the hazard of malaria transmission. On the other hand, mosquitoproofing and the destruction of adult mosquitoes are immediately effective in this respect. Detailed instructions regarding the environmental control measures discussed below will be found in TM 5-632/NAVDOKS TP-Pu-2/AFM 85-7.

- (1) *Selection of camp and base sites.* Since the effective flight range of *Anopheles* mosquitoes rarely exceeds 1 mile, sites should be located at least 1 mile from any known reservoir of malaria or from any large breeding area of *Anopheles* mosquitoes.
- (2) *Mosquitoproofing.* Mosquitoproofing includes not only screening of doors and windows but also closure of all other openings through which *Anopheles* mosquitoes might gain entrance. In malar-

ious areas, all buildings or tents in which personnel eat, sleep, work, or congregate at night should be mosquitoproofed.

- (a) *Screening of doors and windows.* Effective screening for *Anopheles* mosquitoes must be 16 or 18 mesh or finer with apertures not larger than 0.0475 inch in diameter. The best grade metal or Fiberglas screening available should be used. Window screens should be full length and securely fastened. Screen doors should open outward, be self-closing and should be strongly constructed so they will not sag or warp. In highly malarious areas it is desirable to have double screen doors separated by a vestibule at least 6 feet in length between them.
 - (b) *Closure of other apertures.* Careful attention must be paid to the closing of all unscreened apertures through which mosquitoes might gain entrance.
 - (c) *Tents.* In malarious areas, all tents, except those used solely for storage, should be equipped with insect screen liners.
 - (d) *Maintenance.* Routine maintenance of mosquitoproofing is essential. Occupying units should make minor repairs as needed.
- (3) *Destruction of adult mosquitoes.* One of the most effective means of promptly breaking the cycle of malaria transmission is the destruction of adult mosquitoes. This may be accomplished with residual sprays, aerosol dispensers, use of fog generators, mist sprayers, and air-plane spraying. Some of the most important malaria vectors have shown physiological resistance to DDT and other commonly used insecticides. In other cases, *Anopheles* vector species have developed behavior patterns which cause them to avoid lethal contact with residual insecticides. Where either of these problems seems to be interfering with control measures, the advice of medical entomologists should be obtained.

(a) *Residual sprays.* The application of an effective residual insecticide to the inside of buildings, tents, and other mosquito-frequented shelters, is highly effective for killing adult mosquitoes which rest on the treated surfaces. The insecticide solution should be applied as a spray to walls, ceilings, screens, and other areas where mosquitoes rest. Special attention should be given to spraying the undersides and backs of furniture and the interiors of closets. Applications should thoroughly wet the surface but not run off. In a malarious area it is frequently advisable to treat all buildings in nearby towns and villages as well as buildings or tents in the military installation. Residual treatments, when carefully applied, are effective for extended periods on surfaces protected from weather.

(b) *Aerosol dispensers.* The issue of self-discharging, low-pressure aerosol dispenser "bombs" is very useful in treating all types of enclosures such as barracks, mess halls, tents, etc., and even occasionally such open shelters as foxholes, caves, and dugouts. The aerosol will give a quick kill of the adults but does not provide any residual effect. It should be used as instructed on the label of the dispenser. If the enclosure is large, the aerosol container should be carried through the area at a normal walking speed while the material is allowed to discharge upward toward the ceiling. Doors, windows, and vents should be closed during application and for at least 15 minutes thereafter.

(c) *Area control.*

1. *Vegetation.* Where the vector species utilize sylvatic resting places, area spraying of vegetation may contribute to the malaria control program. Barrier zones may be established around bivouac areas, observation posts, gun emplacements, etc., by spraying vegetation in a strip sur-

rounding the area to be protected. Liquid formulations of effective insecticides made from water-wettable powders or emulsifiable concentrates and applied with a mist blower or power sprayer with mist nozzles will yield a short residual effect. Oil solution sprays may also be used but it should be noted that heavy applications of oil solutions will kill vegetation. Where vegetation is intended for human or animal consumption the advice of technical personnel should be obtained before insecticides are applied.

2. *Area control with mist blowers or fog machines.* Temporary relief from adult mosquitoes may be secured in open areas by the use of insecticidal fog or mist. Regularly scheduled fogging or misting is frequently desirable to supplement residual and larval treatments. Fogging and misting cannot substitute for proper larviciding or residual spraying. To be effective, fogging or misting must be done during calm weather (wind under 5 miles per hour), at night, or early in the morning, in order to prevent too much dispersion of the insecticide by thermal updrafts. For detailed information on fogging and misting, see TM 5-632/NAVDOKS TP-Pu-2/AFM 85-7.

(3) *Control of mosquito breeding.* Mosquito breeding may be eliminated or at least greatly reduced by such measures as drainage, filling, stream clearance, larviciding, elimination of artificial containers of water, fluctuation of the levels of impounded waters, removal of marginal vegetation, intermittent drying, and the introduction of certain species of fish.

(a) *Drainage.* It is important that fixed installations have suitable antimosquito drainage integrated with the usual system designed to carry surface runoff. Drainage should be undertaken early, preferably during the construction pe-

riod. Construction activities, as far as possible should be planned and controlled to prevent the creation of excessive or unnecessary mosquito breeding places.

(b) *Filling.* It is usually necessary to do a considerable amount of filling on the site of new permanent construction. The decision to fill, drain, or larvicide depends entirely on local conditions including permanency of the installations, cost of each type of control, and funds available.

(c) *Stream clearance.* Control of mosquito breeding in marginal pools and in collections of floatage in otherwise freely running streams and canals require that stream margins be straightened and emergent vegetation cleared. Marginal pools may be filled or may be drained by connecting them with the main stream.

(d) *Larvicides.* It is frequently not feasible to drain or fill mosquito breeding areas, but very satisfactory control can be obtained by the use of larvicides. Oil solutions, emulsions, water-wettable powders, and dusts of effective larvicides may be used. When properly applied, larvicides will cause no plant damage and the dosage rate is so small the damage to beneficial organisms is insignificant. Detailed instructions on the preparation and application of larvicides can be found in TM 5-632/NAVDOKS TP-Pu-2/AFM 85-7.

(e) *Miscellaneous measures.*

1. *Shuicing.* In those areas where the anopheline vectors are stream-breeders, they may be controlled by the use of siphon dams or lift gates, by which water is impounded and then is periodically and suddenly released to flush away the larvae.

2. *Drying.* Where irrigation water in rice fields or canals is a source of mosquito breeding, effective control is sometimes possible by interrupting the supply of water so that the fields

become just dry enough each week to remove the surface film of moisture without drying the roots of the plants.

3. *Water level fluctuation.* Periodic fluctuation of water level in ponds or reservoirs is sometimes very effective in controlling mosquito breeding by preventing growth of shore line vegetation favorable to the larvae.

4. *Small containers.* In some areas, routine attention must be given to artificial breeding places such as wells, cisterns, bottles, roof gutters, household water containers, discarded tires, metal cans, and coconut shells. These may be screened, emptied, destroyed, or treated with a larvicide as indicated.

h. Personal protective measures. These measures are defined as those that the individual himself must apply.

(1) *Bed nets.* *Anopheles* mosquitoes are essentially night biters and can bite more easily when a man is asleep and motionless. It is essential that all troops in a malarious area be equipped with and, when feasible, use mosquito bars during seasons of mosquito prevalence. FM 21-10 and AFM 160-46 illustrate and describe the proper utilization of bed nets.

(2) *Protective clothing.* When mosquitoes are prevalent, all personnel should wear clothing that will protect them from mosquitoes when they are outside of screened and residually sprayed inclosures. Properly worn protective clothing should consist of long trousers tucked into boots, and long-sleeved shirts, buttoned at the neck, with sleeves rolled down. In certain areas head nets may be desirable.

(3) *Chemical repellents.* The insect repellent is effective against *Anopheles* mosquitoes. The repellent should be carefully applied over all exposed surfaces of the body (except lips and eyes) and to clothing where it is stretched over the body, as over shoulders, buttocks, and ankles. Application to the skin should be repeated every 2 to 6 hours as needed.

(4) *Avoidance of unnecessary exposure.*

(a) *Local villages.* Highly malarious areas such as unprotected towns or villages should be avoided as much as possible. It may be desirable to place such areas OFF LIMITS during hours of darkness if a high incidence of malaria exists.

(b) *Swimming.* Swimming and bathing out of doors after sundown should be prohibited in areas where there is a risk from malaria-carrying mosquitoes.

i. *Cooperation with local health authorities.*

Most cases of malaria are acquired while troops are associated with the infected indigenous population. Therefore, it is imperative that every effort be made to assist the local health authorities in implementing an effective malaria control program else much of the value of the military control program is nullified.

j. *Chemoprophylaxis.*

(1) The combined chloroquine-primaquine tablet (0.300 gram of chloroquine base and 0.045 gram of primaquine base) will be used for malaria chemoprophylaxis, regardless of malaria species, in all areas where malaria is endemic. Such medication should be given by roster under the general supervision of an officer and the direct supervision of noncommissioned officers on the same day of the week *after* a meal. Chloroquine is active against the asexual forms of all malaria parasites and thus is used to decrease the chances of clinical disease appearing. Primaquine acts to destroy the exoerythrocytic or tissue forms of *P. vivax* and *P. malariae*, thereby preventing a late relapse. In most areas of the world the administration of one such tablet given *on the same day of each week is adequate*. The dosage should not be increased or modified without the prior approval of the appropriate Surgeon General. Administration of the drug should be started at least 1 day prior to entering the endemic area. Individuals leaving the en-

demic area should continue their weekly medication for a minimum of 6 weeks, and preferably for 8 weeks.

(2) This suppressive medication is employed only as an adjunct to, and not a substitute for, the various other methods of protection against malaria as described.

(3) Some few individuals will develop a transient anemia shortly after the initiation of the chloroquine-primaquine tablets. This is related to a deficiency of glucose-6-phosphate-dehydrogenase (G6PD) in their erythrocytes, rendering the cells somewhat more susceptible to hemolysis by primaquine. Mild compensatory hyperplasia of the bone marrow follows and continued administration of the drug is tolerated. Very rarely the hemolysis is sufficiently severe to produce a transient jaundice and such people require careful clinical evaluation.

(4) *LARGER AMOUNTS OF PRIMAQUINE MAY PRODUCE SEVERE TOXICITY. THE CHLOROQUINE-PRIMAQUINE COMBINATION TABLET HAS NO PLACE IN THE TREATMENT OF OVERT MALARIAL DISEASE.*

k. *Malaria Discipline.* There is only one general measure of malaria control applicable to all situations and to all individuals. This approach to malaria prevention is best described as *malaria discipline*. Malaria discipline implies constant and intelligent application of personal protective measures by the individual. Without malaria discipline, all other control measures fall short. All control programs must begin with and must continuously emphasize this aspect. In counterinsurgency or limited warfare operations, particularly in jungle areas, personal protective measures may be the only methods available for protection of troops against malaria infection. In such situations, where environmental control measures are difficult or impossible to apply, the individual soldier must be constantly aware of the danger of malaria infection, and must conscientiously use the measures available for his personal defense against infection with malaria parasites.

APPENDIX I

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APPENDIX II

GLOSSARY OF TERMINOLOGY OF MALARIA*

- Attack.**—Period of acute (overt) illness consisting of a single paroxysm or of several separate paroxysms. The first attack following the incubation period is called the "primary attack."
- Autochthonous.**—Term applies to malaria contracted locally.
- Benign tertian.**—Colloquial name for *vivax* malaria.
- Blackwater fever.**—Fever, often severe or fatal, characterized by acute intravascular hemolysis with hemoglobinuria; believed to be due to repeated infection with *falciparum* malaria and often precipitated by the taking of quinine. Sometimes called "hemoglobinuric fever."
- Case, collateral.**—In malaria eradication terminology, a case occurring in the immediate vicinity of a malaria case which has been the subject of an epidemiological investigation (may be specified as collateral fever case, collateral suspected case, etc.). This is the equivalent of the epidemiological term "contact" used in many infectious diseases, which would be inaccurate in malaria where infection does not spread by contact.
- Chemoprophylaxis.**—Protection from or prevention of disease by chemotherapeutic means.
- Crescent.**—Common term for the gametocytes of *P. falciparum*.
- Cure, clinical.**—Relief of symptoms of a malaria attack (e.g., by chemotherapeutic action against asexual erythrocytic parasites) without complete elimination of the infection.
- Cure, radical.**—Complete elimination of the malaria parasite from the body so that relapses cannot occur. Radical cure may be brought about by natural means in the absence of specific medication (natural or spontaneous cure), by radical treatment, or by suppressive cure.
- Cure, suppressive.**—Complete elimination of the parasite from the body by means of continuous suppressive treatment.
- Endophagy.**—Tendency of mosquitoes to feed indoors.
- Endophily.**—Tendency of mosquitoes to rest indoors, whether by day or by night.
- Erythrocytic.**—Developing within red blood cells; applied to stages of the malaria parasite.
- Exflagellation.**—Extrusion and liberation of microgametes (flagella) by male gametocytes.
- Exoerythrocytic.**—Developing in tissues outside the red blood cells; applied to stages of the malaria parasite in the vertebrate host. Abbreviated EE.
- Exogenous malaria.**—Malaria transmitted by outdoor-biting mosquitoes.
- Exophagy.**—Tendency of mosquitoes to feed outdoors.
- Exophily.**—Tendency of mosquitoes to rest outdoors, whether by day or by night.
- Gamete.**—Mature sexual form, male or female. In malaria parasites the female gametes (macrogametes) and male gametes (microgametes) normally develop in the mosquito.
- Gametocyte.**—Parent cell of a gamete. In malaria parasites, the female gametocytes (macrogametocytes) and male gametocytes (microgametocytes) develop in the red blood cell. Very young gametocytes cannot usually be distinguished from trophozoites.
- Gametocytocide.**—Drug which destroys the sexual forms of malaria parasites.
- Gametocytogenesis.**—Formation of gametocytes.
- Hemoglobinuric fever.**—Synonym of *blackwater fever*.
- Latent period.**—Stage during which malarial infection in the vertebrate is not evidenced clinically by any symptoms of disease; occasionally used for the condition in which few or no parasites can be detected by microscopic examination. There is normally a latent period preceding the primary attack ("incubation latency") and a period or periods of latency between the relapses following the primary attack, when the erythrocytic forms have disappeared from the blood but infection persists.
- LC₅₀.**—Abbreviation for median lethal concentration.
- LD₅₀.**—Abbreviation for median lethal dose.
- Macrogamete.**—Female gamete.
- Macrogametocyte.**—Female gametocyte.
- Malaria, benign tertian.**—Synonym for *vivax* malaria.
- Malaria, bromeliad.**—Malaria transmitted by species of *Anopheles* that breed in certain bromeliaceous plants in South and Central America.
- Malaria, cerebral.**—Form of pernicious malaria associated with cerebral symptoms and due to infection with *Plasmodium falciparum*.

*For a more comprehensive glossary see Terminology of Malaria and Malaria Eradication, WHO, Geneva, 1963.

Malaria, chronic.—Colloquial term for the state of ill health associated with prolonged and repeated malaria infection. Its use is not recommended.

Malaria, congenital.—Malaria infection directly transmitted from mother to child; such infection is relatively rare and usually takes place *in utero* through the placenta (prenatal or true congenital malaria), but it is believed that it may also occur at delivery. The term "hereditary malaria" is not recommended.

Malaria, falciparum.—Malaria infection caused by *Plasmodium falciparum*.

Malaria, malariae.—Improper term for malaria infection caused by *Plasmodium malariae*. The correct term is "quartan malaria."

Malaria, ovale.—Malaria infection caused by *Plasmodium ovale*.

Malaria, pernicious.—Malaria infection with severe symptoms, usually due to *Plasmodium falciparum*.

Malaria, quartan.—Colloquial name for malaria infection caused by *Plasmodium malariae*. This term is preferred to "malariae malaria."

Malaria, simple tertian.—Synonym for *vivax* malaria.

Malaria, subtertian.—Synonym of *falciparum* malaria.

Malaria, tertian.—Synonym of *vivax* malaria.

Malaria, tropical.—Synonym of *falciparum* malaria. Also known under the obsolescent name of "aestivo-autumnal malaria."

Malaria, vivax.—Malaria infection caused by *Plasmodium vivax*.

Malignant tertian.—Obsolescent term for *falciparum* malaria.

Maturation.—Final stage in the formation of the macrogamete, by which it is prepared for union with the microgamete.

Merozoite.—Product of segmentation of a tissue schizont, or of an erythrocytic schizont before entering a new host cell. Merozoites are found either separated from or contained in the original schizont.

Microgamete.—Mature male gamete.

Microgametocyte.—Male gametocyte.

Oöcyst.—Fertilized female cell (zygote) after encystment, developing in malaria parasites from the oökinete.

Oökinete.—Motile vermicle stage of the malaria parasite, following fertilization of the macrogamete and preceding oöcyst formation.

Ovarian stages.—In the mosquito, the progressive changes in the ovary and ovarioles during oögenesis, representing degrees of development of the oöcytes and variously classified by different authors.

Parasitemia.—Condition in which malaria parasites are present in the blood. If this condition in the human subject is not accompanied by pyrexia or other symptoms of malaria except for a possible enlargement of the spleen, it is known as asymptomatic parasitemia, and the person exhibiting the condition is known as a symptomless parasite carrier. Asymptomatic parasitemia may be primary (occurring before primary-attack symptoms) or secondary.

Parasite clearance time.—Time elapsing from the first drug administration to the first occasion on which no parasites can be demonstrated in the blood.

Parasite count.—Number of parasites per cubic millimeter of blood on a given slide.

Patent period.—Stage during which malarial infection in the vertebrate is evidenced by the presence of parasites in the blood. A subpatent period is sometimes distinguished during which parasites are believed to be present in the blood in very small numbers but are not detectable by normal microscopic examination.

Periodicity.—Recurrence at regular intervals of symptoms in malaria, characterized clinically by paroxysms and resulting from the invasion of the blood by new generations of parasites. Periodicity may be quotidian, tertian, quartan or double-quartan according to the intervals between paroxysms.

Phase, extrinsic.—That part of the life cycle of *Plasmodium* occurring in the arthropod vector.

Phase, intrinsic.—That part of the life cycle of *Plasmodium* occurring in the vertebrate host.

Plasmodium.—Generic name of the parasites of human malaria.

Pre-erythrocytic.—Existing before the infection of erythrocytes; applies to exoerythrocytic stages of *Plasmodium* developing from the sporozoites. See also *schizogony*.

Prepatent period.—Early stages of malarial infection in the vertebrate, before the invasion of erythrocytes is microscopically detectable.

Prophylaxis.—Any method of protection from or prevention of disease; when applied to chemotherapy it is commonly designated "drug prophylaxis" or "chemoprophylaxis."

Prophylaxis, causal.—Complete prevention of erythrocytic infection by the administration of drugs that destroy either the sporozoites or the primary tissue forms of the malaria parasite.

Prophylaxis, clinical.—Synonym of suppressive treatment.

Quartan.—Recurring every third day (every 72 hours). Recurrence on two successive days, with 1-day free intervals, is known as double-quartan periodicity. See also malaria *quartan*.

Quotidian.—Recurring daily.

Recrudescence.—Renewed manifestation of infection (short-term relapse) believed due to survival of erythrocytic forms. Not to be confused with *recurrence*.

Recurrence.—Renewed manifestation of infection (long-term relapse) believed due to reinfection of erythrocytes from exoerythrocytic forms. Not to be confused with *recrudescence*.

Reinfection.—Establishment of a fresh infection after a previous similar infection has died out or has been eliminated by treatment.

Relapse.—Renewed manifestation (of clinical symptoms and/or parasitemia) of malarial infection separated from previous manifestations of the same infection by an interval greater than those due to the normal periodicity of the paroxysms. Relapses are sometimes classified as recrudescences and recurrences; they can be either clinical or parasitic, the latter being evidenced only by the reappearance or increase in number of the parasites in the blood. The qualifications "short-term" and "long-term" may be used to designate relapses fol-

lowing the primary attack after intervals of less than 2 or more than 6 months, respectively.

Repellent.—Any substance which produces a negative response in mosquitoes, causing them to avoid a close approach such as alighting on the skin of the animal host or entering a room sprayed with the substance.

Ring form.—Annular form of young trophozoites of malaria parasites in blood cells.

Romanowsky stain.—Mixture of eosin, methylene blue, and methylene azure which stains differentially the various elements of malaria parasites.

Rosette.—Colloquial name for some types of mature schizont.

Schizogony.—Asexual process in the malaria parasite involving the production of erythrocytic or exoerythrocytic schizonts. The stages of schizogony occurring in cells other than erythrocytes in the vertebrate host ("exoerythrocytic schizogony") are divided into (a) primary EE forms ("pre-erythrocytic stages," "primary tissue forms"), in which EE forms are present before the erythrocytes are normally invaded; and (b) secondary EE forms ("exoerythrocytic forms *sensu stricto*" "paraerythrocytic stages," "secondary tissue forms"), in which EE forms are present after the erythrocytes are normally invaded.

Schizont.—Intracellular asexual form of the malaria parasite, developing either in tissue or in blood cells. The nuclei of schizonts show evidence of schizogonic division. The schizonts are qualified as mature when the nuclei and the cytoplasm are fully divided so that the merozoites have taken shape; erythrocytic schizonts are then called "segmenters" or (colloquially) "rosettes."

Schizonticide.—Drug which destroys the asexual forms of malaria parasites. Schizontocides are distinguished as blood schizontocides and tissue schizontocides. When "schizonticide" is used alone, it usually refers to a blood schizonticide, i.e., one which acts on the erythrocytic asexual parasites. Tissue schizontocides are those drugs which destroy the exoerythrocytic stages of the parasite. If they act on the primary exoerythrocytic forms they are referred to as primary tissue schizontocides ("causal prophylactic drugs"); if on the secondary forms, as secondary tissue schizontocides.

Schüffner's dots.—Fine, evenly distributed granulations brought out by suitable staining in red cells infected with *P. vivax* and *P. ovale*. The granulations seen in *Plasmodium ovale* infections are better known as James' stippling.

Segmentation.—Schizogonic division of malaria parasites leading to the formation of merozoites.

Segmenter.—Mature erythrocytic schizont.

Sporadic.—Term applied to malaria when autochthonous cases are too few and scattered to cause any appreciable effect on the community. These cases are often due to relapses of a previous infection: for purposes of epidemiological classification by origin of infection, the term "relapsing" is then preferred.

Sporogony.—Process of development occurring in the mosquito which follows sexual union of gametes and ends with the formation of sporozoites.

Sporontocide.—Drug which, when given to the malaria-infected vertebrate host, prevents or interrupts the development of the parasite in mosquitoes feeding on that host. Also known as "antispogonic drug."

Sporozoite.—Final stage of sporogony of *Plasmodium* in the mosquito; the infective form of the malaria parasite occurring either in a mature oöcyst before its rupture or in the salivary glands of the mosquito.

Sporulation.—Strictly, production of spores by multiple cell fission; incorrectly used for *schizogony*.

Superinfection.—Fresh infection brought about in a host while a previous infection with a parasite of the same species is still present.

Suppression.—See under *treatment, suppressive*.

Susceptibility.—1. Liability in a population of insects to be killed by a particular insecticide. The average susceptibility of a species or population of mosquitoes is usually measured in terms of the median lethal concentration (LC_{50}). 2. Liability of a species of mosquito to become infected when fed on a person known to be infectious; usually measured in relation to the liability of infection of another species fed at the same time on the same person. 3. Liability of a person to become infected. The lower the immunity, the higher the susceptibility.

Tertian.—Recurring every other day (every 48 hours). See also *malaria, tertian*.

Tissue stages.—Schizogonic stages of malaria parasites occurring in cells other than erythrocytes in the vertebrate host. See also *exoerythrocytic schizogony*.

Treatment, antirelapse.—Treatment aimed at the prevention of relapses, particularly long-term relapses.

Treatment, presumptive.—Administration of an antimalarial drug or drugs, usually in a single dose, in suspected malaria cases before the results of blood examinations are available. Its principal objectives are relief of clinical symptoms and prevention of transmission.

Treatment, radical.—Treatment adequate to achieve radical cure. In *vivax*, *malariae*, and *ovale* infections, this implies the use of drugs which destroy the secondary tissue stages of the parasite.

Treatment, suppressive.—Treatment aimed at preventing or eliminating clinical symptoms and/or parasitemia by early destruction of erythrocytic parasites. It does not necessarily prevent or eliminate the infection, and overt malaria may develop after drug withdrawal.

Trophozoite.—Strictly, any asexual and growing parasite with undivided nucleus. In malaria terminology, generally used to indicate intracellular erythrocytic forms in their early stages of development. Trophozoites may be in either a ring stage or an early amoeboid or solid stage, but always have the nucleus still undivided.

Zygote.—Product of the union of the male and female gamete; term formerly used incorrectly to designate the oöcyst.

APPENDIX III

SYNTHETIC ANTIMALARIAL DRUGS AND THEIR SYNONYMS

(From W.H.O. Technical Report Series No. 226, 1961)

4-aminoquinolines

		<i>*Amodiaquine</i> (Dihydrochloride)	
Cam-aqi	Flavoquine		
Camoquinal	Miaquine		
Camoquine	SN 10751		
		<i>*Amopyroquine</i> (Dihydrochloride)	
Propoquine	PAM 780		
		<i>Cycloquine</i>	
Ciklochin	Halochin		
		<i>*Chloroquine</i> (Diphosphate)	
Aralen	Resochin		
Avloclor	Resoquine		
Bemaphate	Sanoquin		
Chinamine	Tanakan		
Gontochin	Tresochin		
Imagon	Trochin		
Iroquine	SN 7618		
Klorokin	Win 244		
Luprochin			
		<i>*Chloroquine</i> (Sulfate)	
Nivaquine	3377 R.P.		
Nivaquine B			

9-aminoacridines

		<i>*Mepacrine</i> (Dihydrochloride)	
Acriquine	Italchina		
Acrichin	Malaricida		
Acrihina	Methoquine		
Arichin	Metaquine		
Anofelin	Metocrine		
Atabrin	Palacrine		
Atebrin	Palusan		
Chemiochin	Pentilen		
Chinaerin	Plasmoquine E		
Crinodora	Quinacrine		
Erion	Tenieridine		
Haffkinine	SN 390		
Hepacrine	866 R.P.		
		<i>Mepacrine</i> (Methanesulfonate)	
		Quinacrine soluble	Atebrin musonate
		<i>Azacrine</i> <i>Aminoacrichine</i> (Dihydrochloride)	

*Proposed International Nonproprietary Names (Prop. I.N.N.).

8-aminoquinolines

<i>*Pamaquine</i> (Methylene-bis-β-hydroxynaphthoate)			<i>*Pentaquine</i> (Monophosphate)
Aminoquin	Praequine	SN 13,276	
Beprochin	Proechin		
Gamefar	Quipenyl		<i>Isopentaquine</i> (Mono-oxalate)
Gametocide	SN 971	SN 13,274	
Plasmochin	4516 R.P.		<i>*Primaquine</i> (Diphosphate)
Plasmoquine		SN 13,272	Neo-Quipenyl
<i>Fourneau 710</i>			<i>Quinocide</i> (Dihydrochloride)
Antimalarine	SN 3115	Chinocid	Win 10,448
Rhodoquine	710 F.	CN 1,115	
Plasmocide			
<i>Certuna</i>			
Cilional	Sele		
Oprochin	SN 191		

Biguanides

<i>*Proguanil</i> (Hydrochloride)			<i>*Chlorproguanil</i> (Hydrochloride)
Balusil	Paludrine	Lapudrine	M 5943
Bigumal	Palusil		
Biguanide	Plasin	M 10 580	<i>Chlorazine</i>
Chlorguanide	Proguanide		
Chloriquane	Tirian		
Diguanyl	SN 12,837		
Drinupal	M 4888		
Guanatol	3359 R.P.		
Lepadina			

Diaminopyrimidines

<i>*Pyrimethamine</i>	
Daraprim	Chloridin
Darapram	B-W 50-63
Erbaprelin	D.R. 16,056
Malocide	4753 R.P.

*Proposed International Nonproprietary Names (Prop. I.N.N.).

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